Thermodynamics of Water–Solid Interactions in Crystalline and Amorphous Pharmaceutical Materials

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Received 21 October 2013; revised 13 November 2013; accepted 15 November 2013

ABSTRACT: Pharmaceutical materials, crystalline and amorphous, sorb water from the atmosphere, which affects critical factors in the development of drugs, such as the selection of drug substance crystal form, compatibility with excipients, dosage form selection, packaging, and product shelf-life. It is common practice to quantify the amount of water that a material sorbs at a given relative humidity (RH), but the results alone provide minimal to no physicochemical insight into water–solid interactions, without which pharmaceutical scientists cannot develop an understanding of their materials, so as to anticipate and circumvent potential problems. This research was conducted to advance the science of pharmaceutical materials by examining the thermodynamics of solids with sorbed water. The compounds studied include nonhygroscopic drugs, a channel hydrate drug, a stoichiometric hydrate excipient, and an amorphous excipient. The water sorption isotherms were measured over a range of temperature to extract the partial molar enthalpy and entropy of sorbed water as well as the same quantities for some of the solids. It was found that water–solid interactions spanned a range of energy and entropy as a function of RH, which was unique to the solid, and which could be valuable in identifying batch-to-batch differences and effects of processing in material performance. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:2772–2783, 2014

Keywords: water sorption; water in solids; hygroscopicity; hydration; thermodynamics; solid state; crystallinity; amorphous

INTRODUCTION

Water sorption of pharmaceutical materials is considered as an important, sometimes critical, factor that affects selection of the salt and crystal form of a drug substance, manufacturing and performance of solid dosage forms. In this honorary edition of Journal of Pharmaceutical Sciences, devoted to Professor George Zografi, it is noted that he along with colleagues and students began to investigate the water sorption properties in the 1970s, building a prototype moisture sorption system to evaluate pharmaceutical materials.[1] In 1988, Prof. Zografi reviewed the critical aspects of water–solid interactions from a fundamental, scientific perspective, highlighting the distinction between adsorption in crystalline and absorption in amorphous solids, capillary condensation, deliquescence, and formation of hydrates[2]—physicochemical factors that continue to challenge the development of drug products 25 years later. Over the years, it has been recognized that water sorption can affect powder bulk density, blending, flow and compaction,[3–5] capsule mechanical properties,[6] tablet hardness,[7–9] disintegration[7,10–12] and dissolution,[10–14] excipient compatibility,[15–17] and chemical stability.[18–20] The moisture properties of pharmaceutical solids are an important part of package selection.[21–23] Many commercial drug products contain a storage statement on the label around moisture protection, and may contain a desiccant or special packaging, underscoring water's relevance to detrimental changes that it can produce on storage.

Most drugs are crystalline solids that generally sorb only a small amount of water from the atmosphere, for example, 0.1%–0.2% water at a relative humidity (RH) as high as 90%. The reason for the low sorption level is that water molecules mainly have access to the solid surface, not to the bulk of crystalline particles. After only a few layers of water molecules deposit onto a surface, the sorbed water properties start to approach that of bulk water, that is, the vapor pressure or RH approaches 100%. For example, if a crystalline solid has a typical specific surface area of 0.5–1 m^2/g, using water's area of 0.10 nm^2/molecule value,[24] one molecular layer would occur at a water content of 0.03%. Considering that multilayers can form before a monolayer is established, it is not too surprising that at a few multiples of 0.03%, the RH will approach 100%, which is consistent with the high humidity water content of crystalline solids in the 0.1%–0.2% range. The important physical perspective is that although the moisture level is small for crystalline solids, water molecules occupy a significant fractional coverage of a solid's surface even at a moderate RH of 50%.

Another important aspect of water sorption is that it can vary from one batch of drug or excipient to another, and in cases where the moisture level is critical, the water sorption profile becomes an important characterization technique for raw materials. There can be energetic and micromeritic reasons for the water sorption level variation. Typically, raw materials are also tested for particle size and specific surface area, and the results can be used to try to normalize the moisture sorption profile by these properties, for example, water content per unit of surface area. It is also possible to analyze a moisture sorption isotherm in terms of the Brunauer–Emmett–Teller (BET) equation to extract a C_B value related to energy of adsorption of the first layer or the Guggenheim-Anderson-de Boer (GAB) equation to extract C_G and K values related to adsorption energies of the first and an intermediate layer.[25,26] Both models also provide the W_m parameter formally related to monolayer capacity, and although it does not provide specific surface areas in accord with values from N_2 gas adsorption, it can have interpretive value.[27] The BET or GAB sorption energy parameters fail to give the complete characterization of a vapor's interaction with

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Journal of Pharmaceutical Sciences, Vol. 103, 2772–2783 (2014)

a solid, in particular water's energetic interaction with a drug or excipient. Specifically, the BET or GAB models do not incorporate interactions between adsorbed vapor molecules, in particular water–water interactions, which presumably are an important factor in the sorption process as the RH increases, especially for the water molecule that exhibits strong H-bonding with itself. Indeed, IR spectroscopic experiments of moisture sorption on NaCl have shown H-bonding of water with itself at submonolayer coverage.[28] It is in fact well established from sorption calorimetry experiments that heats of sorption vary continuously as the vapor pressure (or RH in the case of water) of the probe increases, indicating that a single energy parameter such as C_{B} can miss important detail in characterizing water–solid interactions.[25,29]

Sorption calorimetry is less commonly used in routine characterization of drug substances and raw materials. In contrast, automated water sorption equipment is a standard technique that requires minimal sample preparation and effort, making it more appropriate for routine characterization. The main data obtained by the water sorption technique is water weight versus RH. Although it is necessary to quantify the water content of materials and the isotherm provides practical value in characterizing their "hygroscopicity,"[30] the isotherm contains far greater information regarding water–solid thermodynamic interactions. In this research, a more detailed analysis of water sorption isotherms is executed. The water sorption isotherms were measured for several anhydrous crystalline solids, an isolated site hydrate, a channel hydrate, and an amorphous polymer. Specifically, the compounds selected represent "nonhygroscopic" anhydrous drugs (genistein, indomethacin, and griseofulvin), the nonhygroscopic excipient lactose monohydrate, the hygroscopic channel hydrate erythromycin A dihydrate, and the hygroscopic amorphous excipient polyvinylpyrrolidone (PVP K29-32). The water sorption isotherm data were analyzed to provide partial molar enthalpy and partial molar entropy of sorbed water, as well as the partial molar quantities for the solid component in the case of PVP and erythromycin A dihydrate. It was the intent of this research (1) to illustrate and execute the methodology and (2) to provide the interpretation of the thermodynamics of pharmaceutical solids with sorbed water.

THEORETICAL BACKGROUND

Crystalline solids are generally thought to adsorb water because of minimal pathways for water to penetrate the particle bulk. However, it is possible that some of the critical distinctions in crystalline materials arise from defects or imperfect crystallinity, which leads to water absorption in addition to adsorption. In this context, the theoretical analysis should not be limited to or assume only adsorption. It is in fact unnecessary and certainly undesirable to make such limiting assumptions in the theoretical analysis.

The chemical potential (μ) of water vapor can be readily calculated from its vapor pressure (p). The most common standard state for sorption studies is water vapor at its saturation vapor pressure p^0. Using this standard state, the chemical potential is

$$\mu = \mu^0 + RT \ln p/p^0 \tag{1}$$

Although this equation calculates the chemical potential of water vapor relative to vapor at the saturation pressure at temperature T, if the water sorption experiment allows equilibrium to be established, the chemical potential of sorbed water is equal to that of the vapor, in which case, the equation also calculates the chemical potential of water in the solid relative to the vapor at p^0. Also, as the chemical potential of pure liquid water is the same as water vapor at saturation (p^0), the equation can be expressed more specifically to denote the condensed phases involved:

$$\mu_{\mathrm{w}} = \mu_{\mathrm{l}}^0 + RT \ln p/p^0 \tag{2}$$

in which w is for sorbed water and l is for liquid water at its saturation pressure p^0. The quantity p/p^0 is also referred to as the water activity (a_{w}), which, in turn, when multiplied by 100 is defined as the RH. In a water sorption experiment, p/p^0 or a_{w} is fixed and the water content of the solid is measured. The p/p^0 value is changed and water content is measured over a range from $p/p^0 = 0$ to typically 0.9. The isotherm establishes the relation of p/p^0 to water content, which in this analysis will use water mole fraction X_{w}.

$$\frac{p}{p^0} = a_{\mathrm{w}} = f(X_{\mathrm{w}}) \tag{3}$$

Thus, the chemical potential of sorbed water can be calculated as a function water composition.

$$\mu_{\mathrm{w}} = \mu_l^0 + RT \ln f(X_{\mathrm{w}}) \tag{4}$$

The relation of chemical potential of sorbed water to composition is important when combined with standard thermodynamic relations that calculate enthalpy and entropy. From the defining relationship for free energy applied to partial molar functions with liquid water as the reference state:

$$\mu_{\mathrm{w}} - \mu_{\mathrm{l}}^0 = \overline{H}_{\mathrm{w}} - H_{\mathrm{l}}^0 - T\left(\overline{S}_{\mathrm{w}} - S_{\mathrm{l}}^0\right), \tag{5}$$

in which H is enthalpy and S is entropy and overbars signify partial molar quantities. The partial temperature derivatives at constant total atmospheric pressure (P, not water vapor pressure p) and water composition then provide the entropy and enthalpy:

$$\left[\frac{\partial\left(\mu_{\mathrm{w}} - \mu_{\mathrm{l}}^0\right)}{\partial T}\right]_{P,X_{\mathrm{w}}} = -\left(\overline{S}_{\mathrm{w}} - S_{\mathrm{l}}^0\right) \tag{6}$$

and

$$\left[\frac{\partial\left[\left(\mu_{\mathrm{w}} - \mu_{\mathrm{l}}^0\right)/T\right]}{\partial(1/T)}\right]_{P,X_{\mathrm{w}}} = \left(\overline{H}_{\mathrm{w}} - H_{\mathrm{l}}^0\right). \tag{7}$$

These equations illustrate how partial molar entropy and enthalpy at the given water mole fraction can be calculated from moisture sorption isotherms at multiple temperatures. Rather than working with chemical potential in Eq. (7), this function when expressed in terms of water vapor pressure yields

$$\left[\frac{\partial \ln p}{\partial(1/T)}\right]_{P,X_{\mathrm{w}}} = \frac{\left(\overline{H}_{\mathrm{w}} - H_{\mathrm{l}}^0 - \Delta H_{\mathrm{vap}}\right)}{R}, \tag{8}$$